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Progressive Extrapyramidal Disorder With Primary Hypogonadism and Alopecia in Sibs: A New Syndrome?

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We report on 2 sibs with consanguineous parents, and an identical progressive extrapyramidal movement disorder with onset in adolescence and associated with progressive alopecia and primary hypogonadism. To our knowledge, this syndrome has not been reported, and probably represents a newly recognized autosomal recessive condition. © 1996 Wiley-Liss, Inc.

KEY WORDS: hypogonadism, alopecia, neurological symptoms, autosomal recessive inheritance

INTRODUCTION

Congenital alopecia associated with neurological manifestations such as mental retardation, epilepsy, or sensorineuronal deafness has been reported and represents a heterogenous group of genetic disorders [Pridmore et al., 1992]. In rare cases, hypogonadism was associated [Crandall et al., 1973; Johnson et al., 1983; Woodhouse and Sakati, 1983; Al-Awadi et al., 1985]. Here, we present 2 sibs with consanguineous parents and a progressive neurological disorder, primary hypogonadism and alopecia with onset in early adolescence.

CLINICAL REPORT

The parents were healthy Caucasians, first cousins once removed. They have 9 children. The 7th child died immediately after birth with severe arthrogryposis. No further data are available on this child. Family history was otherwise unremarkable.

Patient 1, a male, is the second child and was born after an uneventful pregnancy. Birth weight was 4.3 kg. He walked at age 11 months. No problems were noted during childhood. At the age of 12 years, progressive learning problems, speech difficulties, and gait disturbance were observed. Also, muscle strength and hand control diminished, resulting in difficulties in fine motor skills such as writing. He was trained vocationally as a plumber.

At age 17 years, he was seen by an endocrinologist for delayed puberty with absence of pubic and facial hair growth and with prepubertal testes and penis. Length was 155 cm (3rd centile = 159 cm), span 166 cm, and weight 52.8 kg (3rd–25th centile). There was pectus excavatum. All other physical findings were normal. Urinary gonadotropins and 17-ketosteroids (3.5 mg/24 hrs, normal value 5–12) were low at that time. Human chorionic gonadotropin (HCG) treatment for a period of 6 months (total dose 20,000 U) resulted in a slight increase in testicular volume and firmness, but not in other secondary sexual features. Urinary 17-ketosteroid levels (2.2 mg/24 hrs) remained low.

A testis biopsy at the age of 18 years showed a normal number of tubules with a slight reduction in diameter, and hyalinization of the tubular wall. The initial stages of spermatogenesis were remarkably abundant, with the appearance of large vacuolar inclusions in the nucleus in some spermatogonia and spermatocyte I cells. Spermatids and spermatozoa were absent. There was a normal number of Sertoli cells. The interstitium was normal, with a normal number of Leydig cells. The finding of highly active first stages of spermatogenesis in this biopsy could be explained by the concomitant HCG treatment.

Subsequent treatment with methyltestosterone resulted in an increase of penile size and amount of pubic and axillary hair. However, this therapy was discontinued for aggressiveness toward female relatives.

Neurological examination at age 17 years showed dystonia of the left arm, and dysarthria. Tendon reflexes were normal. Electroencephalogram (EEG) and results of electromyography, spinal fluid, and ophthalmological examinations were normal.

Progressive alopecia was observed in his early 20s. At the age of 47 years, head circumference (OFC) was 54 cm (25th centile). The neurological process had progressed. He was able to walk only a short distance. He could produce only a few vocal sounds and had difficulties eating and drinking. His uncontrolled movements were dystonic and choreoathetotic, especially of the upper limbs. Tendon reflexes were normal. Babinsky reflex was plantar. There was scoliosis and pectus excava-

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tum. Eye movements and hearing were normal. There was pronounced atrophy of the facial muscles and alopecia, including sparse eyebrows and eyelashes (Fig. 1). There was also atrophy of the interosseous muscles of both hands. He was a social, good-natured man. He could understand a simple conversation, but his reactions were often inappropriate. His build was gynoid. Testicular volume was 12 ml bilateral. Axillary and pubic hairs were sparse. Skin and nails were normal.

A karyotype on peripheral blood lymphocytes was normal 46,XY after high resolution G-banding. Serum copper was 87 μg/dl (normal 80–140) and serum ceruloplasmin 25 mg/dl (normal 20–55). Serum testosterone was 380 ng/dl (normal 300–1,000 ng/dl), serum follicle-stimulating hormone (FSH) 8.3 mIU/ml (normal 2–10), and luteinizing hormone (LH) 4.9 mIU/ml (normal 2–10). Scanning electron microscopy (SEM) of scalp hair showed longitudinal grooves in some of the hair shafts, but no specific abnormalities (Fig. 2). Brainstem evoked auditory responses and peripheral sensory and motor nerve conduction velocities (ulnar and median nerve) were normal. Somatosensorial evoked responses and magnetic resonance image (MRI) of the brain could not be interpreted satisfactorily, due to artifacts from involuntary movements. However, there appeared to be a generalized process affecting the central white matter on MRI.

Patient 2 is the sister of patient 1 and the 5th child in this family. Learning difficulties were noted in primary school and she received special education. At age 14 years, a progressive gait disturbance, mainly of the right leg became evident. She became wheelchair bound in her early 20s. Around the age of 14, a slowly progressive dysarthria and alopecia developed. There was primary amenorrhea, with no development of secondary female sexual characteristics. Electromyography at the age of 19 years was normal.

At the age of 42 years, she weighed 44 kg. OFC was 51.3 cm (3rd centile = 52.2). Length could not be assessed properly, given a severe scoliosis. She was unable to walk and could not sit unsupported. Speech was unintelligible. Movements were uncontrolled, with choreoathetotic and dystonic movements of the upper limbs with the head constantly held in hyperextension. Eye movements were normal. Hearing was normal and she was able to understand a simple conversation. There was alopecia of the scalp, with absence of eyelashes (mainly of the lower eyelids) and sparse eyebrows. Her facial appearance was very similar to that of her brother (Fig. 3). There was also atrophy of the small muscles of the hands. Pubertal score was A1M1P2-3 according to Tanner. Some pubic hair appeared in the last few years.

Karyotype on peripheral blood lymphocytes was normal 46,XX. Serum estradiol levels were low, 14 pg/ml (normal value more than 30 in early follicular phase). Serum FSH was 46.1 mIU/ml (postmenopausal value) and LH was 14.3 mIU/ml (normal value 2–10 mIU/ml).

DISCUSSION

We present 2 sibs with a syndrome of progressive extrapyramidal movement disorder, dementia, progressive alopecia, primary hypogonadism, and microcephaly in one of them. This is most likely an autosomal recessive trait.

The neurological symptoms included abnormalities of muscle tone and posture with involuntary choreoathetotic and dystonic movements. This resulted in gait problems, scoliosis, absence of hand function, dysarthria, and difficulties with swallowing. Onset of the neurological symptoms was in early adolescence and progressed more rapidly in the female patient. Thirty years after the onset of the symptoms, the male patient was still able to walk short distances, but there

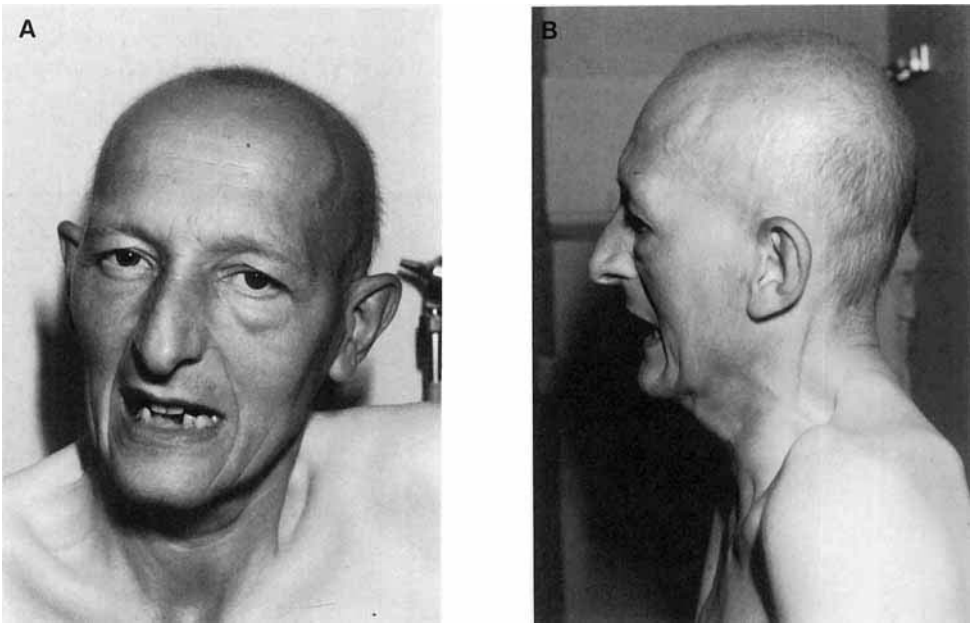

Fig. 1. **A,B:** Facial appearance of patient 1 at the age of 47 years. Note alopecia, wasting of facial muscles, and dystonic muscle contractions.

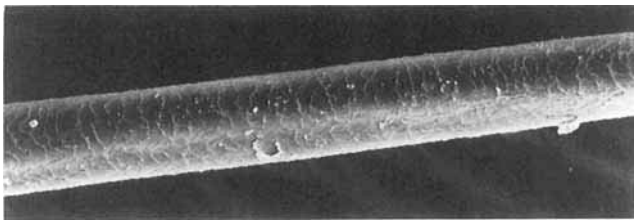

Fig. 2. Scanning electron microscopy of scalp hair in patient 1. Note longitudinal grooves.

was still progression of the disorder. This neurological picture is reminiscent of Hallervorden-Spatz and Wilson's disease, suggesting a pathological process affecting the basal ganglia. Neuroimaging (MRI scan) of the brain did not yield satisfactory results, due to movement artifacts. However, there appears to be a generalized process affecting the white matter. In addition to these signs, patient 2 had microcephaly, suggesting an early onset of the neurological process, before the neurological symptoms occurred. The learning problems in these patients therefore probably represented the first expression of the disorder.

Both sibs presented hypogonadism with pubertal delay and low serum levels of sex steroids. As with the neurological manifestations, this was more pronounced in the female patient, who had complete failure of sexual development. In the male patient, partial pubertal development was obtained after testosterone treatment, and later in life low normal testosterone levels were present with normal gonadotropins. In the female patient, serum estradiol levels were low with elevated gonadotropin levels. These elevated FSH and LH levels are the result of ovarian failure. Hypogonadism can be caused by either a primary gonadal or a hypothalamic-pituitary dysfunction. In the present patients, normal or elevated gonadotropin serum levels demonstrate a normal hypothalamic-pituitary function. A primary gonadal dysfunction is further supported by the lack of clinical significant effects of gonadotropin treatment in patient 1, whereas progression of pubertal development was obtained by testosterone treatment. A testicular biopsy in patient 1 showed the presence of early stages of spermatogenesis and hyalinization of the tubules, which is a nonspecific finding. Both sibs had normal hair until the second decade, when progressive hair loss occurred. Structurally, nonspecific findings of longitudinal grooves in the hair shafts were present.

The pathogenesis of this disorder is unknown. The slowly progressive neurological manifestations with onset later in life suggest a neurodegenerative disorder. Abnormal storage in the involved tissues (neurons, hair, and gonads) might explain both the progressive nature and diversity of affected tissues (central nervous system, hair, and gonads). However, on the testis biopsy at the age of 18 years, there was no evidence of abnormal storage.

As far as we know, the association of alopecia, hypogonadism, and a progressive extrapyramidal movement disorder as seen in these 2 sibs has not been described. Three sibs of consanguineous parents with hypergonadotropic hypogonadism and alopecia were reported by Al-Awadi et al. [1985]. In 2 other families, hypergonadotropic hypogonadism and alopecia were associated with diabetes mellitus, mental retardation, and mild sensorineuronal deafness [Woodhouse et al., 1983]. Alopecia with hypogonadotropic hypogonadism was reported as an autosomal dominant condition associated with anosmia and conductive deafness but also as an autosomal recessive condition, in which case it was associated with neurosensory deafness [Johnson et al., 1983; Johnston et al., 1987; Crandall et al., 1973]. Alopecia with mental retardation is a heterogenous autosomal recessive condition for which recently a further subdivision has been proposed depending on the presence of either microcephaly and/or epilepsy [Pridmore et al., 1992]. In all aforementioned reports,

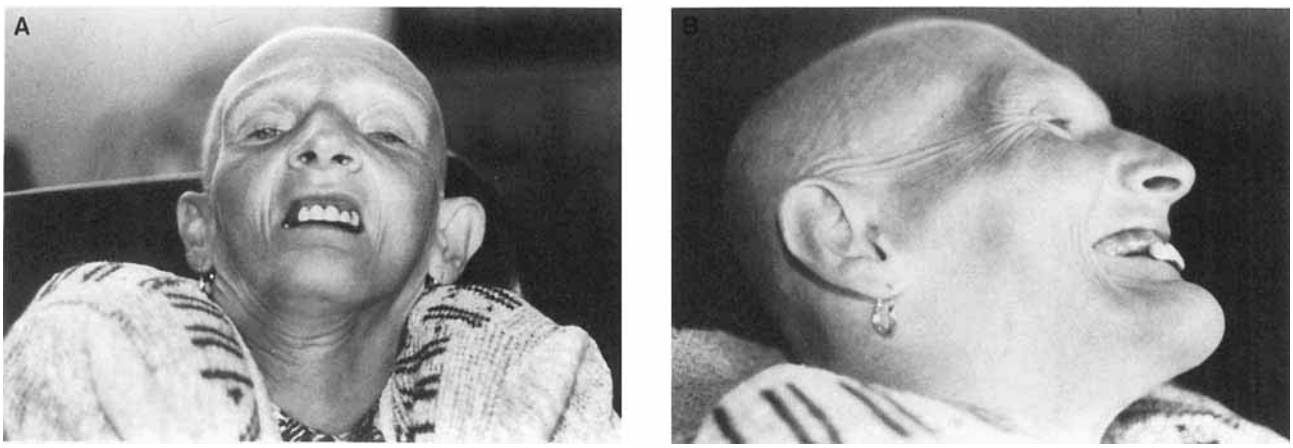

Fig. 3. **A,B:** Facial appearance of patient 2 at the age of 42 years. Alopecia and wasting of facial muscles, with head constantly held in hyperextension.

the alopecia was congenital, and no progressive extrapyramidal neurological disease was present, suggesting a different pathogenesis from the patients reported here.

One patient with adolescent-onset ceroid lipofuscinosis with extrapyramidal and cerebellar signs, associated with hypergonadotropic hypogonadism has been reported [Nass et al., 1986]. This was not associated with alopecia. The neurological findings in these 2 sibs might be compatible with Kufs disease (adult type of neuronal ceroid lipofuchsinosis—MIM 204300). However, as far as we know, primary hypogonadism and alopecia have never been reported in Kufs disease. In addition, no inclusions were seen in lymphocytes nor were curvilinear bodies present in the testicular biopsy of the affected male.

In conclusion, the 2 sibs in this family represent a hitherto undescribed probably autosomal recessive neurodegenerative disorder, associated with alopecia and primary hypogonadism.

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